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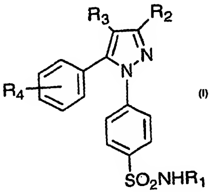
(54) Title: NOVEL CO-CRYSTALS BETWEEN POLYETHYLENE GLYCOLS AND 5-PHENYLPYRAZOLYL-1-BENZENE-SULFONAMIDES



(I)

(57) Abstract: This invention relates to novel and unexpected co-crystals between polyethylene glycols (PEGs) and 5-phenylpyrazolyl-1-benzene-sulfonamides of formula (I).

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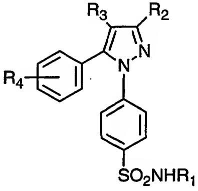
NOVEL CO-CRYSTALS BETWEEN POLYETHYLENE GLYCOLS AND 5-PHENYLPYRAZOLYL-I-BENZENESULFONAMIDES

BACKGROUND OF THE INVENTION

Field of Invention

This invention relates to novel and unexpected co-crystals between polyethylene glycols (PEGs) and 5-phenylpyrazolyl-l-benzenesulfonamides of Formula I.



Formula I

Background Art

5-Phenylpyrazolyl-l-benzenesulfonamides of Formula I constitute a novel synthetic class of compounds with potent COX-2 inhibitory activity useful for the treatment of arthritis and other conditions due to inflammation as disclosed in U.S. Pat. No. 5,521,207, which is incorporated herein by reference. The inventors have found that compounds of Formula I form novel co-crystals with PEGs.

SUMMARY OF THE INVENTION

The co-crystals between PEGs and 5-Phenylpyrazolyl-l-benzenesulfonamides of Formula I have lower melting points than pure drug crystals. Further, these co-crystals exhibit physical stability at ambient conditions because of their crystalline nature. This contrasts with the physical instability of solid dispersions of amorphous solids that have been used to improve drug dissolution. [See for example: M. Yoshioka, B.C. Hancock, and G. Zografi. Crystallization of indomethacin from the amorphous state below and above its glass transition temperature. J. Pharm. Sci. 83: 1700-1705 (1994); L. Yu. Amorphous pharmaceutical solids: Preparation, characterization and stabilization. Adv. Drug Delivery Rev. 48:27-42 (2001); and M.

Lovrecich, F. Nobile, F. Rubessa, G. Zingone. Effect of ageing on the release of indomethacin from solid dispersions with Eudragits. Int. J. Pharm. 131:247-255 (1996)].

In one aspect, the present invention provides a co-crystal of a compound of Formula I with a PEG. In another aspect of the invention, in the compound of Formula I, R_1 is H, R_2 is haloalkyl, and R_3 is hydrogen. In another aspect of the invention, the PEG is selected from the group of PEG 400, PEG 600, PEG 800, and PEG 1000. In yet another aspect of the invention, the co-crystal comprises 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and a PEG. In a further aspect of the invention, the co-crystal comprises 4-[5-(3,4-difluorophenyl)-3-(rtifluoromemyl)-lH-pyrazol-l-yl]benzenesulfonarnide and a PEG. In yet a further aspect of the invention, the co-crystal comprises 4-[5-(2,4-difluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and a PEG.

In another aspect of the invention, a process is provided for preparing the co-crystals of the present invention. In another aspect, the co-crystals are made by a method comprising a) dissolving a compound of Formula I and a polyethylene glycol in a solvent; b) allowing the solvent to evaporate; and c) collecting the resulting crystals.

In yet another aspect of the invention, the co-crystals are made by a method comprising a) mixing a compound of Formula I and a polyethylene glycol in water; b) stirring the mixture of Step a for about one to 21 days; c) collecting the resulting crystals; and d) washing the crystals with a solution comprising the compound and a suitable. solvent.

In a further aspect, the invention provides a pharmaceutical composition which comprises a co-crystal of a compound of Formula I with a polyethylene glycol. In another aspect of the invention, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier or excipient.

Still another object of the present invention is to provide a method for preventing or treating inflammatory conditions in mammals by administering to said mammals a co-crystal of a compound of Formula I with a polyethylene glycol.

A further object of the present invention is to provide a method for producing a medicament using a co-crystal of a compound of Formula I with a polyethylene glycol. These, and other objects, will readily be apparent to those skttled in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Powder X-ray diffraction (PXRD) patterns of amorphous 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide: a) initial pattem; b) pattern after 5 days at ambient conditions; and c) pattern after 14 days at ambient conditions.

Figure 2. (PXRD) patterns of 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG 400 co-crystal: a) initial pattern; b) pattem after 5 days at ambient conditions; and c) pattern after 14 days at ambient conditions.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "co-crystal" means a composition comprising two compounds which form a crystal in which both compounds are integral parts of the crystal.

The term alkyl, unless otherwise specified, where used either alone or within other terms such as "haloalkyl", "alkoxyalkyl", and "hydroxyalkyl", embraces linear, branched, or cyclic radicals having one to 20 carbon atoms, or preferably one to about twelve carbon atoms, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals. A saturated alkyl group is one having the maximum amount of hydrogens possible, .that is, no double bonds. Examples of. saturated hydrocarbon radicals include groups such as methyl, ethyl, n-propyl, .isopropyl, n-butyl,. tbutyj, .isobutyl,_secrbutyl,.cyclohexyl,_(cyclohexyl)ethyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(l,4-pentadienyl), ethynyl, I- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. A "lower alkyl" is a shorter chain alkyl or group, having eight or fewer carbon atoms.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two

hydrido radicals may be attached to a carbon atom to form a methylene (--CH_2-) radical.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl, and 4-methylbutenyl. The terms "alkenyl", "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "halo" means halogens such as fluorine, chlorine, bromine, or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. A monohaloalkyl radical, for example, may have either an iodo, bromo, chloro, or fluoro atom within the radical. Dihalo radicals may have two of the same halo atoms or a combination of different halo radicals. Trihaloalkyl radicals would have three of the same halo atoms or a combination of different halo radicals. Polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, difluorochloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, and dichloropropyl. The term "halomethyl" would be an example of a haloalkyl. The term perhaloalkyl embraces haloalkyl compounds in which all available valence positions are occupied by halogens.

The.terms. ".alkoxy"jembraces linear_orjbranched.oxy-CQntaining.radicals, attached through oxygen, each having alkyl portions of one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy, and tert-butoxy.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to six carbon atoms attached through sulfur. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio, and hexylthio.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes -CO_2H.

The term "carboxyalkyl" embraces alkyl radicals substituted with a carboxy radical and may be additionally substituted on the alkyl radical with halo. Examples of

such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl, and carboxypropyl.

The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Examples of such lower alkoxycarbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, and hexyloxycarbonyl.

The term "aminoalkyl" embraces alkyl radicals substituted with one or more amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like.

The term "alkylamino" denotes amino groups that have been substituted with one or two alkyl radicals having alkyl portions of 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino, and the like.

The term "arylamino" denotes amino groups, which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical.

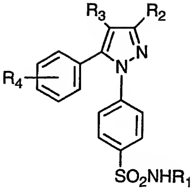
The term "aminocarbonyl" denotes an amide group of the formula $-C(=O)NH_2$. The term "alkylaminocarbonyl" denotes an aminocarbonyl group that has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "lower N-alkylaminocarbonyl" and "lower N,N-dialkylaminocarbonyr' radicals with lower alkyl portions as defined above.

The. .term "arninosulfonyr'.de_notes .a_sulfonarnide.group_pftheiormula $-SO_2NH_2$.

The term polyethylene glycol (PEG) means a condensation polymer of ethylene glycol with the general formula $H(-OCH_2CH_2-)_nOH$ or $HOCH_2(CH_2\theta\, CH_2)_nCH_2OH$.

Description of the Invention

The inventors have found that compounds of Formula I,



Formula I

wherein R_1 is selected from H or C_{1-4} alkyl; R_2 and R_3 are independently selected from the group consisting of H, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, cyano, nitro, formyl, carboxyl, and alkoxycarbonyl; R_4 represents one to three substitutents independently selected from the group consisting of H, C_{1-4} alkyl, C_{1-4} haloalkyl, cyano, nitro, and halogen; form novel co-crystals with PEGs. Preparation of the compounds of Formula I is achieved by procedures described in U.S. Pat. No. 5,521,207.

The co-crystals of the present invention exhibit physical stability at ambient conditions and therefore provide stable formulations, tablets, powders, and the like.

Inflammatory conditions in mammals may be prevented or treated by administering to a mammal in need of such treatment a compound of Formula I with a polyethylene glycol. In practice, the amount of the compound to be administered ranges from about 0.001 to 100 mg per kg of animal body weight, such total dose being given at one time or in divided doses.

Eor_use_as an..anti=inflammatory-agentin-animals thejnv.entive-.composition may be administered either orally or by injection. Where it is desired to administer the inventive composition in a dry, solid unit dosage form, capsules, boluses, or tablets containing the desired amount of active compounds usually are employed. These dosage forms are prepared by intimately and uniformly mixing the active ingredient with suitable finely divided diluents, fillers, disintegrating agents, and/or binders such as starch, lactose, talc, magnesium stearate, vegetable gums, and the like. Such unit dosage formulations may be varied widely with respect to their total weight and content of the anti-inflammatory agent depending upon factors such as the type of host animal to be treated, the severity and type of inflammation, and the weight of the host.

Alternatively, the anti-inflammatory compositions of the present invention may be administered to animals parenterally, for example, by intraruminal, intramuscular, or subcutaneous injection in which event the active ingredients are dissolved or dispersed in a liquid carrier vehicle. For parenteral administration, the active materials are suitably admixed with an acceptable vehicle, preferably of the vegetable oil variety such as peanut oil, cottonseed oil, and the like. Other parenteral vehicles such as organic preparations using solketal, propylene glycol, glycerol formal, and aqueous parenteral formulations are also used, often in combination in various proportions. The active compound or compounds are dissolved or suspended in the parenteral formulation for administration; such formulations generally contain from about 0.005 to about 5% by weight of the active compound.

Preparation of co-crystals

Method 1. The co-crystals of this invention are prepared by evaporation of a solution of a suitable PEG and a compound of Formula I in a suitable solvent. Non-limiting examples of suitable solvents include water, alcohols such as methanol, ethanol, isopropanol, and the like. Suitable PEGs include PEG 200, PEG 300, PEG 400, PEG 600, PEG 800, PEG 1000, and the like. The molar ratio of PEG to a compound of Formula I in the crystallization solution is from about 0.5 to 1 to about 10 to 1 at a temperature of about 5°C to about 30°C.

Method 2. The co-crystals of this invention may also be prepared by stirring a compound of Formula I in a mixture of an appropriate PEG and water. The ratio of water to PEG can be from about 1:2, v:v to about 1:3. v:v. The solid obtained is filtered and the crystals are washed with a near-saturated solution of the compound in a suitable solvent to remove excess PEG. Suitable solvents include, but are not limited to, water, methanol, isopropanol, and the like, or mixtures thereof.

Examples

It is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to perform the various processes of the invention and are to be construed as merely illustrative and not limitations of the preceding disclosure in any way

whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures and techniques.

Preparation 1: Preparation of the amorphous form of 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)- 1H-pyrazol- 1-yl]benzenesulfonamide.

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide was heated in a drying oven at 180 °C until completely melted. The hot melt was then removed from the oven and stored at 5°C for 30 minutes to give a glassy solid. X-ray diffraction showed no intensive diffraction peak and therefore the solid was amorphous.

Procedure 1: Single crystal X-ray analysis

Data were collected on Bruker SMART 6K CCD X-ray area detector with window diameter = 13.5 cm controlled by a Windows 2000 based PC computer with SMART version 5.625 software (Bruker, 2001), at low temperature (120°K), with graphite-monochromatized *CuKa* radiation [λ(*CuKa*)= 1.541 8A]. Alternatively, data were collected using a Rigaku RAXIS RAPID imaging plate area detector with detector aperture = 45.0 x 25.6 cm. It was controlled by a Windows 2000 based PC computer with Rapid Auto version 1.06 software (Rigaku, 2000), at low temperature (120°K), with Micromax-02 micro-Confocal mirrors Cu-Ka radiation [*X(CuKd)* = 1.5418 A].

For data collected by the Bruker detector, all reflections were measured in six image groups with 606 frames in each group; the exposure time was five seconds per frame. Among-thenvthree ·groups-of images were collected at 2Θ= -40° and the other-three groups were at 2Θ= -80° which makes the $2\theta max$ = 133.07°. The sample / detector distance was 5.073 cm. The data reduction program, SAINT+ version 6.22 (Bruker, 2001), was used to determine the Laue group and for structure solution and refinements. The structure was solved by direct methods, using SHELXS version 6.12 (Bruker, 2001). For data collected by the Rigaku detector, indexing was performed from three 3° oscillations frames that were exposed for 180 seconds. All reflections were measured in five image groups with six frames in each group; the exposure time was 60 seconds per degree. Among them, five groups of images were at angles phi=0°, 90°, 180°, 270° with chi=50°and phi=0° with chi=0° all frames were delta omega =30°, and which makes the $2\theta max$ = 136.3°. The sample/detector distance was

12.74 cm. The data reduction program, Rapid Auto version 1.06 (Rigaku, 2000), was used for determining the Laue group and for structure solution and refinements.

Results of the crystal data are summarized in Tables 1-13.

Procedure 2: X-ray powder diffraction analysis

Powder X-ray diffraction analysis (PXRD) was performed using a Scintag X2 Advanced Diffraction System (controlled by Scintag DMS/NT 1.30a and Microsoft Windows NT 4.0 software). The system uses a Copper X-ray source (45 kV and 40 mA) to provide CuKa $_1$ emission of 1.5406A and a solid-state Peltier cooled detector. The beam aperture was controlled using tube divergence and anti-scatter slits of 2 and 4 mm and detector anti-scatter and receiving slits of 0.5 and 0.2 mm width. Data were collected from 2 to 35° two-theta using a step scan of 0.037step with a counting time of one second per step. Scintag round, top loading aluminum sample holders with a 12 mm diameter cavity were utilized for the experiments. Powders were packed into the holder and were gently pressed by a glass slide to ensure coplanarity between the sample surface and the surface of the sample holder.

Procedure 3: Infrared spectra

IR data were collected from 4000 → 400 cm^{-1} at 4-cm^{-1} resolution on a Nicolet 760 spectrometer equipped with a TGS detector. Sensitivity, expressed as instrument gain, was 2. Data were processed as a Fourier transform utilizing a Happ-Genzel apodization function and plotted as % transmittance *vs.* frequency. The final spectra .were.the-sum.of-200individual .scans.

Example 1. Preparation of 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG 400 co-crystal: (Method 1)

PEG 400 (130.8 mg) and 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide (133.3 mg) were dissolved in 1 mL of ethanol to obtain a clear solution in a 10 mL glass vial. The molar ratio between PEG 400 and 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)- lH-pyrazol- 1-yl]benzenesulfonamide was 1.1:1 in the solution. The vial was placed in a fume-hood at ambient temperature to allow evaporation of ethanol. Diamond shaped crystals were obtained after two days. Single crystal X-ray data are given in Tables 1 and 2.

Example 2. Preparation of 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG 400 co-crystals: (Method 2)

A mixture of 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide (4.82 g) and 20 mL PEG 400 and water (2: 1, v:v) was stirred for two weeks. The solid was filtered and washed using a solution of 60 mg/mL 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide in isopropanol. The significant diffractions (major characteristic peaks) of the PXRD pattern are listed in Table 3. The infrared spectrum (potassium bromide pellet) shows significant absorbtions at 3277,2892, 1610, 1594,1556, 1497, 1470, 1448, 1409, 1373, 1355, 1306, 1271,1295, 1236, 1201, 1172,1130,1110, 977, 839, 821,776,750, 733, 626, 610, 564, 544, and 481 cm^{-1}.

Example 3. Preparation of 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG 400 co-crystals

Following the procedure of Example 1 but substituting 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide for 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide a co-crystal was obtained. Crystal data are given in Tables 4 and 5.

Example 4. Preparation of 4-[5-(3,4-difluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG 400 co-crystals

Following the procedure of Example 1 but substituting 4-[5-(3,4-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide for 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide a co-crystal was obtained. Crystal data are given in Tables 6 and 7.

Example 5. Preparation of 4-[5-(2,4-difluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG 400 co-crystals

Following the procedure of Example 1 but substituting 4-[5-(2,4-difluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide) for 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide) a co-crystal was obtained. Crystal data are given in Tables 8 and 9.

Example 6. Preparation of 4-[5-(4-fluorophenyl)-3-(txifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG 600 co-crystal

PEG 600 (73.6 mg) and 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide (205.4 mg) were weighed into a glass vial. Ethanol (2 mL) was added to the vial to form a clear solution. The vial was placed in a fume hood to allow evaporation of ethanol at room temperature. Crystal data are given in Tables 10 and 11.

Example 7. Preparation of 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG 1000 co-crystals

PEG 1000 (88 mg) and 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide (205.7 mg) were weighed into a glass vial. Ethanol (2 mL) was added to the vial and was slightly heated to form a clear solution. The vial was then placed in a fume hood to allow evaporation of ethanol at room temperature. The resulting crystals were analyzed using single crystal X-ray diffraction. Crystal data are given in Tables 12 and 13.

Example 8. Stability of 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG 400 co-crystals versus amorphous form of 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)- lH-pyrazol- l-yl]benzenesulfonamide

Samples of the co-crystals of Example 1 and the amorphous form of 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide were held at ambient temperature (20-25?C). Powder X-ray diffraction patterns were taken at Day 1 (initial), Day 5, and Day 14. As the spectra shown in Figure 1 demonstrate, the amorphous form was unstable. Diffraction peaks are observable after storing the amorphous solid for 5 days at ambient conditions and are more intense after 14 days. As shown in Figure 2 the co-crystal was stable for at least 14 days.

Example 9. Compaction studies

Samples of 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide (150 - 190 mg) were compressed using flat-faced punches with 10/32" diameter. Compaction forces were 1000, 1500, 2000, and 3000 lbf. After being ejected from the die, tablets were subjected to diametrical pressure using a

hardness tester. AU tablets of non-PEG containing powder laminated, i.e., fracture planes were roughly parallel to the tablet faces. However, for tablets of the PEG co-crystals, all tablets fractured diametrically, i.e., fracture planes ran through the center of the tablet and were roughly perpendicular to the tablet faces. No obvious lamination was observed.

Table 1. Crystal **data for 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG-400 co-crystal at 120 ^{0}K**

Molecular formula	$C_{16}H_{11}F_4N_3O_2S$• ~1/3 H(OCH2CH2)$_n$OH
Molecular weight	~518
Space group	P2(1)/n
a (Å)	12.1824(5)
b (Å)	10.6122(5)
c (Å)	18.0355(8)
β (°)	101.095(2)
Unit cell volume (Å^3)	2288.09(18)
Calculated density (g/cm^3)	1.502
Z	4

Table 2.. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG-400 co-crystal. **U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.**

	x	y	z	U(eq)
0(1)	12381(2)	4676(3)	721(2)	41(1)
S(1)	12526(1)	5575(1)	1320(1)	32(1)
F(4)	5748(2)	3661(2)	2015(1)	49(1)
O(2)	13430(2)	6450(2)	1413(2)	39(1)
N(2)	8331(3)	8555(3)	1014(2)	28(1)
F(1)	7846(2)	12045(2)	138(2)	64(1)
C(5)	9292(3)	6602(3)	805(2)	27(1)
C(4)	9321(3)	7804(4)	1106(2)	27(1)
F(2)	7030(3)	12215(2)	1060(2)	80(1)

N(3)	8404(3)	9787(3)	816(2)	32(1)
F(3)	6107(2)	11625(3)	-2(2)	84(1)
C(3)	10322(3)	8337(4)	1462(2)	34(1)
N(I)	12660(3)	4801(3)	2100(2)	40(1)
C(I)	11276(3)	6455(4)	1226(2)	26(1)
0(4)	3834(4)	227(3)	1708(2)	82(1)
C(9)	7235(3)	8188(4)	998(2)	28(1)
C(7)	7341(3)	10179(4)	675(2)	30(1)
C(15)	7026(4)	5345(4)	2199(2)	38(1)
C(16)	7406(3)	6449(4)	1939(2)	35(1)
C(ll)	6903(3)	6950(4)	1253(2)	29(1)
C(6)	10264(3)	5930(4)	872(2)	27(1)
0(5)	1866(4)	1709(3)	1570(2)	76(1)
C(2)	11298(3)	7660(4)	1513(2)	35(1)
O(3)	4491(3)	-1550(3)	2890(2)	68(1)
C(13)	5601(3)	5212(4)	1078(2)	35(1)
C(12)	5992(3)	6322(4)	829(2)	33(1)
C(14)	6126(4)	4752(4)	1756(2)	37(1)
C(8)	6597(3)	9231(4)	770(2)	34(1)
C(1O)	7092(4)	11509(4)	459(3)	41(1)
C(20)	4916(6)	94(7)	2156(4)	85(2)
C(25)	735(6)	1932(6)	1228(4)	93(2)
C(23)	2475(7)	1567(6)	1018(3)	84(2)
C(22)	3685(7)	1459(6)	1388(4)	95(2)
C(19)	5106(5)	-1224(6)	2344(4)	86(2)
C(17)	4853(5)	-2747(6)	3180(4)	86(2)

Table 3.

Major Characteristic PXRD Peaks of the 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l- yl]benzenesulfonamide and PEG 400 Co-crystal

Two-Theta Angle* (degree)	d-Spacing (Angstrom)
16.84	5.26
19.18	4.62
19.61	4.52
21.29	4.17
22.17	4.01
24.27	3.66
25.72	3.46

*: ±0.10°

Table 4. Crystal data for 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG 400 Co-crystal at 120 ^{0}K

Molecular formula	$C_{16}H_{11}ClF_3N_3O_2S$ • ~1/3 H(OCH2CH2)$_{8.7}$OH
Molecular weight	~535
Space group	P2(1)/c
a (Å)	8.3421(12)
b (Å)	29.918(4)
c (Å)	11.3860(15)
β (°)	110.392(7)
Unit cell volume (Å^3)	2663.6(6)
Calculated density (g/cm^3)	1.441
Z	4

Table 5. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x *l*ß *)* for 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG-400 co-crystal). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(I)	11254(5)	3424(1)	2600(3)	39(1)
C(2)	10399(4)	3253(1)	1424(3)	39(1)
C(3)	9308(5)	2891(1)	1279(3)	41(1)
C(4)	9098(5)	2703(1)	2330(3)	38(1)
C(5)	9977(5)	2869(1)	3515 (4X	45(1)
C(6)	11060(5)	3233(1)	3659(4)	43(1)
C(7)	7570(5)	1644(1)	2555(4)	44(1)
C(8)	6299(5)	1757(1)	1420(4)	44(1)
C(9)	6602(5)	2192(1)	1206(3)	41(1)
C(IO)	7828(6)	1217(1)	3242(4)	52(1)
C(H)	5565(5)	2495(1)	203(4)	42(1)
C(12)	5079(5)	2915(1)	465(4)	46(1)
C(13)	3998(5)	3184(1)	-475(4)	48(1)
C(14)	3420(5)	3020(1)	-1690(4)	46(1)
C(15)	3879(5)	2606(1)	-1971(4)	46(1)
C(16)	4936(5)	2340(1)	-1028(3)	43(1)
C(17)	-5007(6)	5149(2)	4467(5)	66(1)
C(18)	-3166(8)	5466(2)	3566(5)	79(2)

C(19)	1331(9)	5510(2)	3722(6)	89(2)
C(20)	1253(8)	5803(2)	5043(7)	94(2)
C(21)	2193(7)	5939(2)	6361(6)	85(2)
C(22)	3139(7)	5704(2)	8480(5)	76(2)
C(23)	2940(6)	5342(2)	9311(5)	68(1)
C(24)	929(6)	4995(2)	10077(4)	60(1)
Cl(I)	2086(1)	3353(1)	-2889(1)	61(1)
F(I)	9477(4)	1111(1)	3804(3)	72(1)
F(2)	7222(4)	1232(1)	4181(3)	81(1)
F(3)	7122(5)	882(1)	2512(3)	97(1)
N(I)	11589(4)	4332(1)	2895(3)	48(1)
N(2)	8032(4)	2322(1)	2205(3)	41(1)
N(3)	8641(4)	1984(1)	3045(3)	43(1)
0(1)	13973(3)	3838(1)	3950(3)	50(1)
0(2)	12985(4)	3926(1)	1650(3)	54(1)
0(3)	-3310(5)	5193(1)	4531(3)	76(1)
0(4)	-509(4)	5756(1)	4844(3)	66(1)
0(5)	2182(5)	5596(1)	7207(3)	74(1)
0(6)	1211(4)	5327(1)	9280(3)	58(1)
S(I)	12613(1)	3893(1)	2782(1)	43(1)

Table 6. Crystal data for 4-[5-(3,4-difluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG-400 co-crystal at 120 ^{0}K

Molecular formula	$C_{16}H_{10}F_5N_3O_2S \bullet \sim 1/3\ H(OCH2CH2)_{8.7}OH$
Molecular weight	~536.7
Space group	P2(1)/n
a (Å)	11.889(1)
b (Å)	10.6258(6)
c (Å)	18.6465(9)
β (°)	98.778(2)
Unit cell volume (Å^3)	2328.0(3)
Calculated density (g/cm^3)	1.15
Z	4

Table 7. Fractional atomic coordinates and equivalent isotropic displacement parameters (A^2X10^3) for (4-[5-(3,4-difluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG-400 co-crystal.

	x	y	z	B(eq)
S(D	0.7671(1)	0.0471(1)	0.13402(6)	4.28(3)
F(I)	0.2074(5)	0.7136(4)	0.1001(3)	9.6(1)
F(2)	0.1146(4)	0.6548(4)	0.0004(3)	11.0(1)
FP)	0.2909(4)	0.6977(4)	0.0107(3)	9.3(1)
F(4)	0.0842(4)	-0.1417(4)	0.1999(3)	9.6(1)
F(5)	0.0184(6)	-0.0848(7)	0.0799(4)	6.7(2)
F(6)	0.2158(7)	-0.0014(7)	0.2743(4)	9.1(2)
0(1)	0.7546(3)	-0.0460(3)	0.0778(2)	5.18(8)
O(2)	0.8606(3)	0.1325(3)	0.1412(2)	5.36(9)
O(3)	0.8147(5)	0.1653(5)	0.3399(3)	8.3(1)
O(4)	0.6157(7)	0.0187(5)	0.3244(3)	9.1(2)
O(5)	0.5503(4)	-0.1544(4)	0.2112(3)	7.4(1)
N(I)	0.7731(4)	-0.0263(4)	0.2104(2)	5.2(1)
N(2)	0.3410(3)	0.3491(4)	0.0955(2)	3.87(9)
N(3)	0.3482(4)	0.4717(4)	0.0752(2)	4.4(1)
C(I)	0.6403(4)	0.1377(4)	0.1221(2)	3.9(1)
C(2)	0.6410(5)	0.2579(5)	0.1519(3)	4.6(1)
C(3)	0.5410(4)	0.3263(5)	0.1444(3)	4.6(1)
C(4)	0.4422(4)	0.2752(4)	0.1061(2)	3.8(1)
C(5)	0.4414(4)	0.1560(5)	0.0763(2)	4.0(1)
C(6)	0.5423(4)	0.0857(5)	0.0852(2)	-3.9(1)
C(7)	0.2396(5)	0.5081(5)	0.0611(3)	4.6(1)
C(8)	0.1632(5)	0.4147(5)	0.0724(3)	4.5(1)
C(9)	0.2306(4)	0.3124(5)	0.0950(3)	4.3(1)
C(IO)	0.2141(6)	0.6438(6)	0.0409(3)	5.8(2)
C(Il)	0.1961(4)	0.1887(5)	0.1205(3)	4.3(1)
C(12)	0.1220(5)	0.1115(6)	0.0777(4)	6.2(2)
C(13)	0.0850(7)	0.0024(7)	0.1061(6)	8.3(2)
C(14)	0.1226(7)	-0.0336(6)	0.1732(6)	7.4(2)
C(15)	0.1933(7)	0.0409(7)	0.2156(5)	6.9(2)
C(16)	0.2353(5)	0.1514(6)	0.1916(3)	5.5(1)
C(H)	0.9283(9)	0.1903(9)	0.3699(6)	10.7(3)
C(18)	0.751(1)	0.1481(8)	0.3935(5)	9.8(3)

C(19)	0.631(1)	0.1392(8)	0.3600(5)	10.2(3)
C(20)	0.4857(8)	-0.1220(8)	0.2650(6)	10.1(3)
C(22)	0.5060(9)	0.011(1)	0.2829(5)	9.9(3)
C(23)	0.9909(9)	0.229(1)	0.3135(7)	10.5(3)

$Beq = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U33(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U23(bb^*cc^*)\cos\alpha)$

Table 8. Crystal data for 4-[5-(2,4-difluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG-400 co-crystal) at 120 ^{0}K

Molecular formula	$C_{16}H_{10}F_5N_3O_2S$ • ~1/3 $H(OCH2CH2)_{8.7}OH$
Molecular weight	~536.7
Space group	P2(1)/n
a (Å)	12.1312(5)
b (Å)	10.7036(4)
c (Å)	18.1182(9)
β (°)	99.073(2)
Unit cell volume (Å^3)	2323.2(2)
Calculated density (g/cm^3)	1.51
Z	4

Table 9. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2X10^3) for 4-[5-(2,4-difluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG-400 co-crystal.

	x	y	z	B(eq)
5(1)	.0.75904.(9)	0.4.455(1).	0.63098(6)	3.19(2)-
F(I)	0.1975(4)	-0.2136(3)	0.6019(2)	7.5(1)
F(2)	0.1236(3)	-0.1520(3)	0.4943(3)	8.2(1)
F(3)	0.2953(3)	-0.2002(3)	0.5164(2)	6.22(9)
F(4)	0.0821(3)	0.6347(3)	0.7051(2)	5.04(7)
F(5)	0.0644(3)	0.3283(3)	0.5191(2)	5.13(7)
0(1)	0.7462(3)	0.5358(3)	0.5723(2)	4.18(8)
O(9)	0.8493(3)	0.3595(3)	0.6386(2)	4.02(8)
N(I)	0.7691(3)	0.5206(4)	0.7088(2)	3.82(9)
N(2)	0.3398(3)	0.1469(3)	0.6006(2)	3.06(8)
N(3)	0.3475(3)	0.0253(3)	0.5807(2)	3.21(8)
C(I)	0.6343(4)	0.3572(4)	0.6218(2)	2.92(9)
C(2)	0.6364(4)	0.2375(4)	0.6518(3)	3.3(1)
C(3)	0.5379(4)	0.1698(4)	0.6467(3)	3.5(1)

C(4)	0.4397(4)	0.2216(4)	0.6096(2)	2.92(9)
C(5)	0.4364(4)	0.3405(4)	0.5791(2)	2.98(9)
C(6)	0.5350(3)	0.4085(4)	0.5864(2)	2.85(9)
C(7)	0.2419(4)	-0.0128(4)	0.5670(2)	3.3(1)
C(8)	0.1659(4)	0.0813(4)	0.5773(2)	3.3(1)
C(9)	0.2322(4)	0.1843(4)	0.5999(2)	3.04(9)
C(IO)	0.2154(4)	-0.1449(5)	0.5444(3)	3.9(1)
C(II)	0.1972(4)	0.3061(4)	0.6267(2)	3.13(9)
C(12)	0.1122(4)	0.3743(4)	0.5862(3)	3.3(1)
C(13)	0.0721(4)	0.4845(4)	0.6101(3)	3.8(1)
C(14)	0.1211(4)	0.5265(4)	0.6786(3)	3.8(1)
C(15)	0.2039(4)	0.4637(5)	0.7229(3)	4.1(1)
C(16)	0.2431(4)	0.3537(5)	0.6967(3)	3.8(1)
0(2)	0.1143(5)	0.0244(4)	0.3274(2)	6.9(1)
0(3)	0.3102(4)	0.1717(4)	0.3406(2)	6.2(1)
0(10)	0.0516(3)	-0.1535(4)	0.2117(3)	5.9(1)
C(17)	-0.0119(7)	-0.1209(6)	0.2673(5)	7.5(2)
C(18)	0.0065(7)	0.0129(7)	0.2857(4)	7.2(2)
C(19)	0.1284(8)	0.1449(6)	0.3613(4)	7.1(2)
C(20)	0.2443(8)	0.1555(6)	0.3957(4)	7.1(2)
C(21)	0.4217(7)	0.1940(7)	0.3745(5)	7.6(2)
C(22)	0.4858(6)	0.2273(6)	0.3157(5)	7.4(2)

$B_{eq} = 8/3\,\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

Table 10. Crystal data for 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG-600 Co-crystal at 120 ^{0}K

Molecular formula	$C_{16}H_{11}F_4N_3O_2S\cdot(OCH2CH2)_3$
Space group	P2(1)/n
a (Å)	12.230(2)
b (Å)	10.637(2)
c (Å)	18.077(4)
β (°)	101.15(3)
Unit cell volume (Å^3)	2307.3(8)
Calculated density (g/cm^3)	1.490
Z	4

Table 11. Fractional Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG-600 Co-crystals. U(eq) is defined as one third of the trace of the orthogonalized UU tensor.

	x	y	z	U(eq)
S(D	7509(1)	9405(1)	1329(1)	35(1)
F(4)	738(2)	11301(2)	2018(1)	52(1)
O(l)	8410(2)	8538(2)	1426(1)	43(1)
0(2)	7366(2)	10304(2)	727(1)	44(1)
F(I)	2851(2)	2924(2)	143(2)	63(1)
F(2)	2011(3)	2766(2)	1058(2)	76(1)
N(2)	3321(2)	6423(3)	1009(2)	32(1)
F(3)	1112(2)	3354(2)	-14(2)	80(1)
C(5)	4282(3)	8372(3)	801(2)	31(1)
N(I)	7627(2)	10182(3)	2107(2)	41(1)
C(15)	2011(3)	9622(3)	2201(2)	39(1)
C(3)	5313(3)	6646(3)	1467(2)	37(1)
C(7)	2334(3)	4798(3)	668(2)	34(1)
N(3)	3395(3)	5190(3)	811(2)	36(1)
C(4)	4312(3)	7172(3)	1101(2)	31(1)
C(I)	6259(3)	8527(3)	1227(2)	31(1)
C(9)	2229(3)	6784(3)	993(2)	32(1)
C(H)	1896(3)	8023(3)	1242(2)	33(1)
C(ĭ 6)	23W(3)	8523(3)	1938(2)	38(1)
C(6)	5252(3)	9049(3)	871(2)	31(1)
C(2)	6282(3)	7314(3)	1521(2)	36(1)
C(13)	598(3)	9758(4)	1074(2)	40(1)
C(12)	986(3)	8646(3)	821(2)	38(1)
C(14)	1117(3)	10215(3)	1757(2)	40(1)
C(8)	1587(3)	5747(3)	763(2)	36(1)
C(IO)	2084(3)	3465(4)	452(2)	43(1)
0(3)	8898(3)	4749(3)	1712(2)	64(1)
0(5)	8116(3)	8280(3)	3440(2)	64(1)
0(4)	9537(2)	6545(3)	2903(2)	60(1)
C(1 8)	9251(4)	8067(5)	3784(3)	68(1)
C(17)	7457(5)	8404(5)	3986(3)	67(1)

C(21)	9960(4)	4888(5)	2157(3)	67(1)
C(19)	9868(4)	7764(4)	3192(3)	67(1)
C(20)	10159(4)	6217(5)	2354(3)	71(1)
C(22)	8725(5)	3518(5)	1392(3)	72(2)

Table 12. Crystal data for 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG-1000 Co-crystals at 120 ^{0}K

Molecular formula	$C_{16}H_{11}F_4N_3O_2S \cdot (OCH2CH2)_3$
Space group	P2(1)/n
a (Å)	12.225(1)
b (Å)	10.6273(8)
c (Å)	18.027(2)
β (°)	101.202(3)
Unit cell volume (Å^3)	2297.4(3)
Calculated density (g/cm^3)	1.49
Z	4

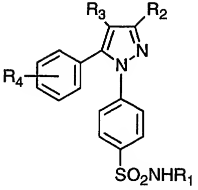
Table 13. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2x l (β) for 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide and PEG-1000 Co-crystals.

	x	y	z	B(eq)
S(D	0.7495(1)	0.4395(1)	0.13357(9)	3.15(4)
F(I)	0.1112(3)	-0.1656(4)	-0.0022(3)	6.4(1)
F(2)	0.2849(3)	-0.2097(4)	0.0141(2)	5.1(1)
F(3)	0.1995(4)	-0.2245(4)	0.1052(2)	6.0(1)
F(4)	0.0736(3)	0.6279(4)	0.2021(2)	4.6(1)
O(l)	0.8397(3)	0.3518(4)	0.1434(2)	3.8(1)
O(2)	0.7584(4)	0.5165(5)	0.2117(3)	5.7(1)
O(3)	0.3106(4)	0.1727(4)	-0.1557(3)	4.6(1)
O(4)	0.4553(4)	0.3453(4)	-0.2088(3)	4.6(1)
0(5)	0.3912(4)	0.5273(5)	-0.3289(3)	4.7(1)
N(l)	0.7357(3)	0.5300(4)	0.0731(2)	2.1(1)
N(2)	0.3310(4)	0.1402(5)	0.1004(3)	2.8(1)
N(3)	0.3387(4)	0.0176(4)	0.0807(3)	2.9(1)
C(I)	0.6243(4)	0.3502(6)	0.1228(3)	2.5(1)
C(2)	0.6294(5)	0.2309(6)	0.1527(3)	3.2(1)
C(3)	0.5294(5)	0.1614(6)	0.1464(3)	3.1(1)
C(4)	0.4306(4)	0.2160(6)	0.1098(3)	3.0(1)
C(5)	0.4273(4)	0.3352(5)	0.0795(3)	2.8(1)
C(6)	0.5258(4)	0.4045(6)	0.0872(3)	2.7(1)
C(7)	0.2329(5)	-0.0211(6)	0.0660(3)	3.4(1)
C(8)	0.1570(5)	0.0744(6)	0.0756(3)	3.1(1)
C(9)	0.2220(4)	0.1772(6)	0.0986(4)	3.2(1)
C(IO)	0.2084(5)	-0.1530(7)	0.0449(4)	3.7(2)
C(H)	0.1886(4)	0.3008(6)	0.1239(3)	2.6(1)
C(12)	0.0987(5)	0.3637(6)	0.0814(4)	3.5(1)
C(13)	0.0586(5)	0.4752(6)	0.1070(4)	3.3(1)
C(14)	0.1118(5)	0.5197(6)	0.1756(4)	3.3(1)
C(15)	0.2001(5)	0.4595(6)	0.2195(4)	4.0(2)
C(16)	0.2392(4)	0.3479(6)	0.1936(3)	3.2(1)
C(17)	0.1245(6)	0.1518(8)	-0.1394(4)	5,1(2)
C(18)	0.2419(6)	0.1618(8)	-0.1009(4)	5.3(2)
C(19)	0.4250(6)	0.1933(7)	-0.1207(5)	5.1(2)
C(20)	0.4865(5)	0.2241(7)	-0.1800(4)	5.1(2)
C(21)	0.5188(6)	0.3801(7)	-0.2638(4)	5.1(2)
C(22)	0.4991(6)	0.5151(7)	-0.2845(4)	4.6(2)

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

What is claimed is:

1. A co-crystal comprising a compound of Formula I



Formula I

wherein R_1 is selected from H or C_{1-4} alkyl;

R_2 and R_3 are independently selected from the group consisting of H, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, cyano, nitro, formyl, carboxyl, and alkoxycarbonyl;

R_4 represents one to three substituents independently selected from the group consisting of H, C_{1-4} alkyl, C_{1-4} haloalkyl, cyano, nitro, and halogen; and a polyethylene glycol.

2. The co-crystal of Claim 1, wherein R_1 is H.

3. The co-crystal of Claim 2, wherein R_2 is haloalkyl.

4. The co-crystal of Claim 3, wherein the haloalkyl is perhalo Ci-C_4 alkyl.

5. The co-crystal of Claim 4, wherein the perhalo Ci-C_4 alkyl is trifluoromethyl.

6. The co-crystal of Claim 2 wherein R_3 is hydrogen.

7. The co-crystal of Claim 1 wherein the PEG is selected from the group of PEG 400, PEG 600, PEG 800, and PEG 1000.

8. The co-crystal of Claim 1 comprising 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide and PEG 400.

9. The co-crystal of Claim 1 comprising 4-[5-(3,4-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide and PEG 400.

10. The co-crystal of Claim 1 comprising 4-[5-(2,4-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide and PEG 400.

11. The co-crystal of Claim 1 comprising 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide and PEG 600.

12. The co-crystal of Claim 1 comprising 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide and PEG 1000.

13. The co-crystal of a compound of Formula 1 and PEG 400 having a space group of $P(2)_1/n$ or $P(2)_1/c$.

14. The co-crystal according to Claim 8 wherein the unit cell dimensions are a = 10-13 Å, b = 9-11 Å, and c = 17-19 Å.

15. The co-crystal according to Claim 8 wherein the characteristic PXRD peaks are

Two-Theta Angle (degree)	d-Spacing (Angstrom)
16.84	5.26
19.18	4.62
19.61	4.52
21.29	4.17
22.17	4.01
24.27	3.66
25.72	3.46

16. A method of making the co-crystal of claim 1 comprising

a) dissolving the compound of Formula I and the polyethylene glycol in a solvent;

b) allowing the solvent to evaporate; and

c) collecting the resulting crystals.

17. The method of claim 16 wherein the compound is 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)- 1H-pyrazol- 1-yl]benzenesulf onamide.

18. The method of claim 17 wherein the polyethylene glycol is PEG 400.

19. The method of claim 17 wherein the polyethylene glycol is PEG 600.

20. The method of claim 17 wherein the polyethylene glycol is PEG 1000.

21. The method of claim 16 wherein the compound is 4-[5-(3,4-difluorophenyl)-3-(trifluoromethyl)- 1H-pyrazol- 1-yl]benzenesulfonamide.

22. The method of claim 2 1 wherein the polyethylene glycol is PEG 400.

23. The method of claim 16 wherein the compound is 4-[5-(2,4-difluorophenyl)-3-(trifluoromethyl)- 1H-pyrazol- 1-yljbenzenesulfonamide.

24. The method of claim 23 wherein the polyethylene glycol is PEG 400.

25. A method of making the co-crystal of claim 1 comprising

a) . mixing-the-compound-ofEormula I and_the.polyethylene glycol in. water;

b) stirring the mixture of step a for about one to 2 1 days;

c) collecting the resulting crystals; and

d) washing the crystals with a solution comprising the compound and a suitable solvent.

26. The method of claim 25 wherein the solvent is isopropanol.

27. The method of claim 25 wherein the compound is 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)- 1H-pyrazol- 1-yl]benzenesulfonamide.

28. The method of claim 27 wherein the polyethylene glycol is PEG 400.

29. The method of claim 27 wherein the polyethylene glycol is PEG 600.

30. The method of claim 27 wherein the polyethylene glycol is PEG 1000.

31. The method of claim 25 wherein the compound is 4-[5-(3,4-difluorophenyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl]benzenesulfonamide.

32. The method of claim 31 wherein the polyethylene glycol is PEG 400.

33. The method of claim 25 wherein the compound is 4-[5-(2,4-difluorophenyl)-3-(trifluoromethyl)- lH-pyrazol- l-yl]benzenesulfonamide.

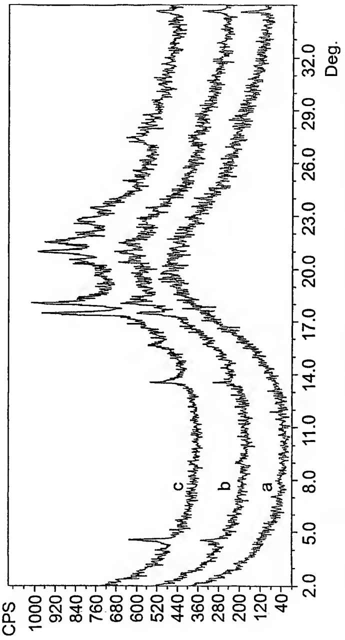
34. The method of claim 33 wherein the polyethylene glycol is PEG 400.

35. A pharmaceutical composition which comprises the co-crystal of claim 1.

36. The composition of claim 35 which further comprises a pharmaceutically acceptable carrier or excipient.

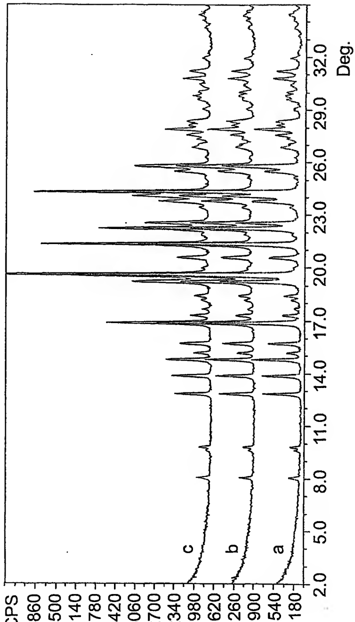
37. A method for preventing or treating inflammatory conditions in a mammal comprising administering to said mammal the composition of claim 35.

FIG. 1



PXRD patterns of amorphous 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide: a) initial; b) Day 5; and c) Day 14.
Deg. = two-theta angle

FIG. 2



PXRD patterns of 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide and PEG 400 co-crystal: a) initial; b) Day 5; c) Day 14.
Deg. = two-theta angle

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/002590

A. CLASSIFICATION OF SUBJECT MATTER
C07D231/12 A61K31/415 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No
A	V. KUSUM DEVI, P. VIJAYALAKSHNII AND M. AVINASH: "Preformulation Studies on Celecoxib with a view to improve bioavailability" INDIAN JOURNAL OF PHARMACEUTICAL SCIENCE, 2003, pages 542-545, XP009056819 the whole document	1-37
A	EP 1 167 355 A (FAKO ILACLARI A.S) 2 January 2002 (2002-01-02) the whole document	1-37

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[x] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex

° Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 November 2005	30/11/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Gregoire, A

International Application No
PCT/IB2005/002590

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	B. M. EL-HOUSIENY YOUSEF: "Thermal investigation on co-crystallization of Ketoprofen with some excipients and the effect of some ionic and non-ionic surfactants on properties of the resultant solid dispersion" J. DRUG RES. EGYPT, vol. 24, no. 1-2, 2002, pages 79-86, XP009056813 the whole document	1-37
A	US 6 492 411 B1 (TALLEY JOHN J ET AL) 10 December 2002 (2002-12-10) the whole document	1-37
P,A	WO 2005/055983 A (MEDCRYSTALFORMS, LLC; GOLDMAN, DAVID) 23 June 2005 (2005-06-23) the whole document	1-37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/002590

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons.

1. [X] Claims Nos :
because they relate to subject matter not required to be searched by this Authority, namely

Although claim 37 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos ·
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be earned out, specifically

3 [ ] Claims Nos ·
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a)

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows.

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3 [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos .

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB2005/002590

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			DE	60100873	D1	06-11-2003
			DE	60100873	T2	22-07-2004
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			ES	2206360	T3	16-05-2004
			HK	1045155	A1	28-05-2004
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			US	2002016351	A1	07-02-2002
US 6492411	B1	10-12-2002	NONE			
WO 2005055983	A	23-06-2005	NONE			